Chapter 4

CENTRAL NERVOUS SYSTEM

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Since lethal amounts of carbon monoxide cause loss of consciousness, there has been a tendency to characterize low levels of carbon monoxide as causing depression of the central nervous system. The threshold level that can exert depression has been difficult to determine. There are several tests of human performance which produce varied results. There are several animal species that have been used also with varying sensitivity to carbon monoxide. Almost all attempts to determine effects of low levels of carbon monoxide have been designed to relate to occupational exposure or environmental ambient content of carbon monoxide. The exposure consists of 8 hours a day, or continuously for 24 hours daily.

The results of prolonged exposure are relevant to establishing the occupational standard and ambient air quality standards for carbon monoxide. However, their relevance to cigarette smoking should be questioned. Since the cigarette smoker is not continuously inhaling cigarette smoke, there is no fixed sustained level of carboxyhemoglobin in a smoker. Furthermore, the levels among smokers are varied, the majority of them ranging between 2 to 8%, with some even reaching 15%. Regardless of variability, it is possible to generalize and formulate the answers to the following questions: Will smokers with carboxyhemoglobin levels as high as 15% suffer from the effects of carbon monoxide? What is the threshold level that does not influence human behavior? According to the experiments that have been properly designed

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and executed, 20% carboxyhemoglobin is the top level of 8-hour exposure that does not affect functional tests of the central nervous system. Almost all smokers show levels considerably less than 20%.

In the consideration of the effects of cigarette smoking on the central nervous system, the pharmacological actions of nicotine are usually ignored. This chapter discusses this subject and points to the beneficial effect on the central nervous system of this possible antagonism between carbon monoxide and nicotine.

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A. Inhalation of Low Levels of Carbon Monoxide Independent of Complexities of Cigarette Smoke

Until 1970, there was considerable confusion concerning the effects of low levels of carbon monoxide on the human performance of psychomotor tests.[1] Since then there has been additional investigation showing that there is no significant depression of the central nervous system at carboxyhemoglobin levels of 20% or less. The results that show negative effects at 20% or less are separated from those which show a depression.

1. No Effect on Human Performance at 20% or Less.

The first investigation of the effects of carbon monoxide on human performance was performed by Forbes et al.[2] in 1946. They tested 8 normal men on their performances in simple tests of reaction times, binocular vision, coordination of the hand and eye. The results of these tests were unaffected by breathing carbon monoxide until their blood was 30% saturated. There was slight impairment in their performance at 45% saturation. Subsequent work has confirmed a lack of effect with levels up to 20% and that levels higher than 20% caused impairment of visual function and manual coordination.

a. Stewart and his collaborators. Human volunteers were exposed to carbon monoxide in concentration of 1, 25, 50, 100, 200, 500 and 1000 ppm for periods of one-half to 24 hours. Exposures producing carboxyhemoglobin saturations greater than 15 to 20% resulted in delayed headaches, changes in

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visual evoked response and impairment of manual coordination. However, levels up to 15 and 20% did not influence the performance testing in time estimation, reaction time, steadiness, manual dexterity, the electroencephalogram and the visual evoked response.[3] The ability to perceive time was not impaired in a range of carboxyhemoglobin saturations of up to 20%.[4,5]

b. Mikulka, O'donnell and their collaborators.[6-9] Human subjects were exposed to 0, 50, 125, 200 and 250 ppm of carbon monoxide for 3 hours. With carboxyhemoglobin levels as high as 12.4%, there were no significant symptoms reported by the subjects. There was also no overall trend toward poorer estimates of 10-second interval and no deterioration of tracking performance. The subjects were also exposed to 75 and 150 ppm of carbon monoxide during sleep for 9 hours. With levels of 5.9 to 12.7% carboxyhemoglobin saturation upon waking, the subjects did not show performance decrements in mental arithmetic, time estimation, tracking, monitoring and visual tests.

2. No Effects on Human Performance at 10% or Less.

a. MacFarland and collaborators.[10-20] The first study reported in 1944 showed that exposure of subjects to carbon monoxide mixtures of up to 20% carboxyhemoglobin influenced vision. There was an impairment in visual threshold when the saturation reached 4 to 5%.[10] In a 1973 study, subjects were exposed to 700 ppm of carbon monoxide until carboxyhemoglobin levels of 6%, 11% and 17% were reached.[20] The subjects were tested as to their

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ability to perform both selected driving-related laboratory tests of visual response and control reactions and over-the-road vehicle driving. Compared to the test results prior to exposure to carbon monoxide, the 6% carboxyhemoglobin level had no effect on driving ability. The 11% and 17% carboxyhemoglobin levels did not appear to seriously affect the ability to drive motor vehicles although there were some statistically-significant differences in some of the tests suggesting some decrement in performance. The earlier results of MacFarland et al. of visual impairment when saturation reached less than 10% has not been confirmed by their recent studies.

b. Guest and collaborators.[21] Eight healthy subjects were exposed to a mixture of carbon monoxide in air to raise carboxyhemoglobin saturations to 10%. In a double-blind study, the exposure did not depress the auditory flutter fusion and critical flicker fusion thresholds. In the same subjects, the oral administration of pentobarbital caused the expected depressant effect on both thresholds.

c. Hanks. Critical tracking task test was used by Hanks in subjects exposed to 0, 25, 50, 75 and 100 ppm for up to 4 1/2 hours. With carboxyhemoglobin levels up to 10%, there was no change in performance of the critical tracking task test.[22]

d. Rockwell and collaborators.[23-25] In four series of experiments in-

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volving 25 human subjects, the exposure to carbon monoxide up to 20% carboxyhemoglobin saturation had the following effects on driving-related tasks. There was no change in gross and fine manual coordination, nor in spatial relational abilities. However, there was a decrease in blink rates and an increase in tracking-lag errors.

3. Effects on Human Performance Below 10%.

The investigators who describe a reduction in human performance even when carboxyhemoglobin levels are below 10% are as follows: Beard and his collaborators who initially reported an influence in performance,[26-29] later denied confirming their results when performed double-blind.[30] The results of Horvath et al.,[31] Schulte,[32,33] Bender et al.,[34,35] Fodor and Winneke,[36] Wright et al.[37] and Groll-Knapp et al.[38] have been disproven by the work discussed above using similar techniques.

4. Electroencephalogram in Man.

Hosko[39] failed to observe any change in the spontaneous electroencephalogram in human subjects exposed to carbon monoxide up to 20%. Grudzinska and Pecora[40] did not report any abnormalities in the electroencephalogram in 60 workers exposed in their work environment to carbon monoxide levels with 5 to 20% carboxyhemoglobin levels. The recording of the electroencephalogram indicates that levels below 20% carboxyhemoglobin do not influence the central nervous system.

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B. Cigarette Smoking

If the carbon monoxide contained in cigarette smoke would influence the central nervous system of the smoker, supportive evidence can be derived by subjecting the same group of subjects to carbon monoxide inhalation and then, to cigarette smoking using the same performance tests described above (see A above). Such a comparison has not been completed. The results relating to cigarette smoking only show signs of stimulation as well as depression of the central nervous system depending on the manner of detection of nervous activity.

1. Electroencephalogram and Sensory Perception.

Philips used computer analysis of electroencephalographic data recorded during resting and working conditions.[41] The effects seen immediately after smoking cigarettes indicate increased alertness, accompanied by facilitation of responses to repeated visual stimulation. The results are significant in that they represent the total response of the central nervous system, confirming the stimulant action of nicotine seen in animals (see C below).

The smoking of cigarettes did not influence the following tests on the eye: pupillary size and glare recovery time,[42] ability to detect objects in simulated night driving conditions,[43] flicker fusion threshold,[44] electroculogram[45] and intraocular pressure.[46] There are reports of transient reduction in peri-

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pheral field of vision following cigarette smoking[47-50] but Krippner and Heimstra[50] question the functional importance of static peripheral activity, i.e. it is not known whether man receives and makes use of static peripheral visual information in dealing with his environment. The same question applies to reported depression of electromyogram[51] and of the patellar reflex seen in smokers.[52]

Differential sensitivity of taste, odor and touch is not significantly different between smokers and nonsmokers.[53] The reported impairment in hearing and reduced pain tolerance seen in smokers compared to nonsmokers[54-59] does not necessarily mean that smoking is the cause of the difference. Seltzer and his collaborators[58,59] have suggested constitutional differences between smokers and nonsmokers as a possible explanation for the effect of smoking on pain perception and hearing loss seen in adult smokers.

2. Performance Tests.

The influence of cigarette smoking was investigated by three groups of investigators who failed to detect any change in the following tests: tracking and loading tasks conducted by Schori and Jones,[60,61] simulated driving task by Heimstra et al.[62,63] and manual dexterity and response time performance by McCune.[64] Cigarette smoking increased arousal which is accompanied by tachycardia.[65-68] Andersson[68] showed that retention of learning was better in the smoking condition than in the nonsmoking condition. Although reaction

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time is shortened 5 min after smoking, the test was significantly faster 40 min and 55 min after smoking, compared to the control measurement before smoking.[69] The biphasic effect of smoking is seen also in animal experiments described in the next section.

C. Interactions Among Carbon Monoxide, Nicotine and Other Drugs

Thus far, this chapter has been reviewing the effects of carbon monoxide separately from cigarette smoking in human performance. The interactions between nicotine and carbon monoxide cigarette smoke have been alsmot entirely ignored by the investigators who have been examining either carbon monoxide alone (see A) or cigarette smoking (see B). Since lethal concentrations of carbon monoxide cause depression of the central nervous system, and lethal injections of nicotine cause convulsions, it is reasonable to suspect that sublethal amounts of both would be antagonistic. A review of the literature indicates that antagonism has been demonstrated by a few techniques in some animal species including man. However, attempts to detect chemical interaction in man are difficult to perform because of complicating factors which are discussed below.

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1. Interactions in Man.

Weber et al. have recently demonstrated that the results of physiological

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functions depend on the degree of activation of the subjects.[70] They examined the effects of low carbon monoxide exposure on the critical flicker fusion technique. In a monotonous situation, carbon monoxide inhalation caused a reduction in test values whereas in an activating situation, the values remained unchanged.

Cigarette smoking and nicotine exert either a stimulation or a depression depending on the mood of the subject; sedation when excited and stimulation when depressed.[71,72] An interaction between carbon monoxide and nicotine will be difficult to detect because of the change in mood of the subject that determines the reaction to the experimental situation. A primary action elicits a secondary action so that identification of the individual effects of carbon monoxide and nicotine will require a complex protocol of experimentation.

a. Carbon monoxide and nicotine. Vestibular nystagmus (lateral movement of the eye during rotation of the body) has been examined by Tibbling to determine any influence of the components of cigarette smoke.[73] She compared the effect of cigarette smoking with intravenous injection of nicotine and smoking of a "nicotine-free" cigarette. However, the subjects were not exposed to carbon monoxide mixture to determine any change in frequency of nystagmus. Her conclusion that nicotine alone is responsible for increase in frequency of nystagmus has not excluded the possibility that carbon monoxide has the opposite effect.

The electroencephalographic changes related to smoking would be a way

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of determining interaction between nicotine and carbon monoxide. However, Hauser et al.[74] noted similar changes in the electroencephalographic pattern while the subject smoked a cotton-filled glass cigarette. The change in dominant frequency of the electroencephalogram has more to do with the act of smoking than any changes due to substances present in the cigarette.

b. Cigarette smoking and caffeine. The effects of caffeine and cigarette smoking on the central nervous system are similar in man. Ashton et al.[75,76] measured the negative shift in the vertex electroencephalogram which occurred prior to an expected stimulus. Both caffeine and cigarette smoking increased the magnitude of the negative shift. Unfortunately, the test did not extend to nicotine or carbon monoxide to determine interaction. The similarity of effects of caffeine and cigarette smoking may help explain the recent observation by Kozlowski[77] that coffee-drinking cigarette smokers take in more nicotine when they reduce their intake of caffeine. However, as the dose of caffeine increases, there is no reduction in nicotine intake. Coffee-drinking cigarette smokers are still able to discriminate between caffeine and nicotine.

Gramberg-Danielsen et al.[78] described another similarity between caffeine and nicotine. Measurements of twilight vision, glare sensitivity and readaptation time are influenced by smoking of cigarettes and by caffeine. There is no information whether or not there is an additive effect of both. There is the possibility that the carbon monoxide contained in cigarette smoke would

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antagonize the effect of caffeine, an interaction that has been demonstrated in animals (see below).

2. Subhuman Primates.

The intravenous injection of nicotine in the squirrel monkey produced an arousal state in the electroencephalogram which is closer to a normal arousal than that induced by caffeine.[79] This technique of recording arousal electroencephalogram would have been ideal to show interaction between inhalation of carbon monoxide and inhalation of cigarette smoke. The exposure of macaca monkeys to 200 ppm carbon monoxide continuously for 100 days did not influence the performance tests.[80,81] The monkeys tolerated 22% carboxyhemoglobin saturation continuously for 100 days, thus verifying the conclusion in man that 20% does not influence the central nervous system.

3. Cats.

Brown and Shryne[82] observed an alert pattern in the electrical activity of the unanesthetized cat following the subcutaneous injection of nicotine. The effects of nicotine, carbon monoxide and cigarette smoke were similar on cortical recordings of the isolated perfused head preparation.[83-85] The responses consisted of cortical activation, behavioral arousal and vasodilation of cerebral blood vessels.

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4. Rats.

Nelsen and Goldstein[86] trained rats on an attention task which required

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them to respond with a single lever press to a very short, variably-presented stimulus for food reinforcement. Treatment with nicotine caused improvement in performance. Morrison and Stephenson[87] observed an improvement in lever-pressing performance in rats treated with nicotine. In his own series of experiments, Erickson[88] concluded that nicotine facilitated the consolidating neural memory trace.

On the other hand, inhalation of carbon monoxide depresses the performance of rats. The threshold exposures that did not influence the central nervous system are as follows: 200 ppm for two hours on reinforced performance,[89] 100 ppm continuously for four days on sleep and waking pattern.[90] Although the effects of higher concentration of carbon monoxide can be antagonized by carbon dioxide,[91] an interaction with nicotine has not been tested.

5. Other Species.

There are reports of stimulant action of nicotine and depression by carbon monoxide in mice,[92-95] rabbits,[96-99] guinea pigs,[100] and pigeons.[101] The dosages of the stimuli and the type of behavioral effects are of such a nature that it is difficult to judge the relevance of the results to humans. The animal experiments did not include interaction between carbon monoxide and nicotine.

D. Practical Aspects of Effects on the Central Nervous System

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A review of the literature reveals that depression of the central nervous system by carbon monoxide is seen only when carboxyhemoglobin levels are

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above 20%. The reports claiming a depression at levels below 10% are questionable and have not been confirmed. Since the majority of cigarette smokers has carboxyhemoglobin levels of less than 5%, a possible influence of carbon monoxide on cerebral function can be excluded. In the few smokers with levels exceeding 10%, any effect of carbon monoxide is likely to be antagonized by nicotine contained in cigarette smoke.

In recent years, there has been a tendency to exaggerate the depressant action of carboxyhemoglobin on human performance. Specifically, it has been suggested that pilots who smoke are likely to perform poorly because of the carbon monoxide contained in cigarette smoke.[102-104] The review of the literature indicates that this is not likely to occur (see A above). Furthermore, nicotine contained in cigarettes improves performance so that antagonism between carbon monoxide and nicotine would be expected to occur (see B above). Thus far, the possibility has been ignored and almost all experiments in man and animals have not been designed to check this possibility (see C above). Additional experiments are needed to test in the same preparation, nicotine, carbon monoxide and cigarette smoke in a manner that would be relevant to the human smoking problem.

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